EXHIBIT A

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Attention:
Brian B. Winegar | Trial Lawyer
Houston: 10000 Memorial Drive, Suite 750 |
Houston, TX 77024-3485
Wyoming: The Tivoli Building|301 W.
Lincolnway | Cheyenne, WY 82001

Re: Rodriguez vs Union Pacific Railroad Company

Dear Mr. Brian Winegar:

Please find a report regarding my opinions on this case below.

1. I am a physician, duly licensed to practice medicine in the State of Illinois. I am Board Certified in Medical Oncology and practice in the fields of Medical Oncology with a subspecialty in Gastrointestinal Oncology, including patients with colorectal cancers from both clinical and research perspectives. I have been involved in these patients' care including various therapies such as in the perioperative and metastatic settings.

   At the University of Chicago, I am the Director of Gastrointestinal (GI) Medical Oncology Program. This entails overseeing a clinical program entailing 6 GI Medical Oncology Faculty members, 3 Advanced Nurse Practitioners, 5 Nurse Navigators, and a Pharmacist, as it pertains to operations of the clinical and research programs within GI Medical Oncology. Annually, we have a census of > 1600 GI cancer patients, of which >350 are new patient and new consultation visits. In addition, I oversee and run the research program entailing 4 clinical trial coordinators, 4 data managers, regulatory personnel, and biobank personnel. The GI research program has more than 30 investigational clinical trials open at the moment. The extends to 3 community satellite centers of the University of Chicago where our studies are available there. As the Director of Interdisciplinary GI Oncology and Assistant Director of Translational Research, this research focus extends to the other oncologic disciplines of GI Surgical Oncology, Radiation Oncology, as well as Anatomical and Molecular Pathology, where I oversee and facilitate cross-discipline collaboration and research.

I have published numerous publications focusing on the management of GI cancers, as well as biologic mechanisms and novel therapeutics of these diseases. I have presented these topics and my research findings internationally at medical conferences and by invitation to academic centers. I have obtained NIH research funding, foundation awards, collaboration with biotech and pharmaceutical companies, and philanthropy to support my work. A primary research focus of mine is on the biological understanding and treatment of gastroesophageal (esophagus, gastroesophageal junction, and stomach) cancers, by studying the normal and oncologic components and molecular pathways of gastrointestinal cells. My research agenda has an overarching goal to validate and improve personalized treatment, immunotherapy, and precision medicine for gastroesophageal cancer and other GI cancers, with findings often relevant to all cancers. A major component of my research is on the quantification of tumor genetic molecular heterogeneity both between individuals with gastroesophageal cancer, but importantly also within a given individual within one tumor site, and from one tumor site to another, and how this impacts personalized targeted therapeutic approaches. To overcome many biological hurdles of the disease that has led to failed therapeutic approaches in the past 1-2 decades, I have designed and executed novel clinical trials to implement treatment strategies based on these laboratory and clinical discoveries.

I serve as a mentor to medical trainees including medical students, internal medicine and surgical residents, as well as medical oncology and surgical oncology fellowship trainees. Most teaching is part of clinical training during clinical care of patients in the inpatient and outpatient setting. I also teach formal didactic lectures to these trainees on the topics of management of various GI cancers. I also teach didactic lectures to first and third year Graduate Students in Cancer Biology regarding the biologic underpinnings of GI cancers and therapeutic strategies.

I serve as associate editor for the *Journal of American Medical Association Network Open* (*JAMA Netw Open*), and I am also on the editorial boards of the *Journal of Clinical Oncology Precision Oncology* (*J Clin Oncol PO*), *Cancer*, and *Cancers*. As associate editor for the Oncology section of *JAMA Netw Open*, I review manuscript submissions pertaining all cancers and from all disciplines (medical, surgical, and radiation oncology) to the journal and determine which manuscripts will be sent for external peer review versus those that would be rejected without review. I then review those manuscripts and external peer reviewer comments and provide a final decision as to whether to reject or accept them paper for publication. As associate editor of *JAMA Netw Open* and member of the editorial boards of *J Clin Oncol PO*, *Cancer*, and *Cancers*, I attend regular board meetings to discuss papers and general operations of the journals. I also serve as an ad hoc reviewer for numerous journals to serve as an external peer reviewer to provide comments and recommendations on acceptance of manuscripts, pertaining to GI cancers, submitted for publication.

I am a member of many medical societies and groups, including the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), the American Association of Cancer Research (AACR). I have participated in consensus guidelines for the treatment of GI cancers for ASCO and other Consortia.

2. I was asked to provide an opinion on exposure of asbestos and its contribution towards causation of Mr. Rodolfo's colorectal cancer and untimely death.

As such, I have reviewed information and records regarding the case of Rodolfo (Rudy) Rodriguez, including the medical records from Big Bend Regional Medical Center and Midland Memorial Hospital regarding his diagnosed *KRAS* mutated colorectal (recto-sigmoid) cancer. I have reviewed the death certificate of Rodolfo Rodriguez having date of death 10/10/2017 and an

indication due to metastatic colon cancer. I have reviewed the letter of Dr. Courtney Crim from 6/11/2020. I have reviewed the depositions of Rito Ortega, Daniel Rodriguez, Diana Rodriguez, Jose Rodriguez, and Rosamaria Gomez Rodriguez. I also reviewed the written report of Mr. Richard Miller. Additionally, I performed a literature review to provide my written report to opine on these topics.

3. Introduction to Cancer:

Cancer is the abnormal and uncontrolled growth of cells in the body.[1] Cancer cells are a distorted version of a normal cell – it is well-established that cancer arises from alteration of one or more cancer-related genes due to change of the DNA sequence and/or changes in the amount of DNA (amplification/deletion), or the expression of the gene itself (through epigenetic changes). Cancer-related genes can be one of two main categories: tumor suppressor genes or oncogenes. Tumor suppressor genes are the 'brakes' in the system, and signal for cells to stop dividing/growing and if there is severe damage to the cell, the signal for it to die (apoptosis or senescence).[2] Oncogenes are the 'gas pedal' of the system, signaling for cells to divide and increase in number, grow in size and also some oncogenes signal the cell to migrate to other areas in the body.[1] Normally, tumor suppressors and oncogenes signal in concert and in equilibrium with each other to maintain a balance, called homeostasis. If there is a wound, nearby cells will be signaled to divide, grow, and migrate to the wound to heal it, but when healed, the cells will return to steady-state. Cancer cells signal to grow inappropriately, due to altered DNA, and behave like a wound that never stops healing. Cancer cells continue to grow inappropriately and the ratio of cell growth to cell death increases, and therefore often cancer masses will form, referred to as 'tumors'. However, some tumors grow as single invasive cells in the absence of classic tumor formation, called diffuse type tumors, such as signet ring gastric cancers.

Although different cancers from different sites and tissues of the body have different sets of altered genes causing the cancer, ultimately, all cancers are caused by alterations in the DNA.[3] These alterations of the DNA within cancer-related genes may be inherited, induced by environmental factors, from random DNA replication errors, or a combination of these factors. A carcinogenesis model has been described for various cancers specifying common genes altered and the sequence in which this occurs over a period of several years. It has been estimated that at least half of the genetic changes occur in precursor cancer cells prior to formation of any tumor mass.

Inherited pathogenic alterations, called germline alterations, can be from a single highly penetrant gene (eg. a tumor suppressor like the APC gene in colorectal cancer),[4,5] or they can be weaker penetrance and also can be multifactorial (multiple causative genes, but each contributing to the develop of cancer to a small degree) and more difficult to discern. A germline event(s) is present prior to the formation of the zygote (the one cell made up of DNA that is half from one parent and half from another parent, also known as a fertilized egg) in the DNA of one (or both) parents. It is estimated that inherited genetic factors are causative or contributory to approximately 5-15% of cancers, depending on the cancer type. Inheriting an altered pathogenic gene usually leads to the onset of a cancer at a younger age, due to the carcinogenesis model shifting earlier in time (ie the cancer development gets a head start right from development).

On the other hand, somatic alterations are those that occur after conception of a zygote, through gestational development, and then after birth and through an individual's lifetime. Somatic genetic alterations can occur from environmental exposures and/or from random DNA replication errors, also referred to as stochastic effects associated with the lifetime number of stem cell divisions within each tissue.

Environmental factors that contribute to the cause of cancer have been described, and can be specific to certain cancer types.[6] Environmental factors include aspects of lifestyle, economic, and behavioral exposures. Chronic inflammation, through various etiologies including infection or other agents, has been associated with carcinogenesis. Poor diet,[7-9] inactivity, and obesity[10] have each been associated with carcinogenesis. Some specific foods are linked to specific cancers. Regardless, any factor that may alter DNA sequence and contribute to carcinogenesis and the ultimate development of cancer can be referred to as a carcinogen. Carcinogens (also referred to as mutagens) are substances or agents that promote DNA changes leading to cancer. Tobacco smoke, for example, is a common and well-known to contain over fifty carcinogens, including nitrosamines and hydrocarbons. In addition to chemicals, radiation and radioisotopes are known carcinogens. Infections with certain viruses, bacteria, and worms are also known carcinogens. Environmental agents such as asbestos are known as carcinogens. Endogenous or exogenous hormones drive cell growth and are known carcinogens. The International Agency for Research on Cancer (IARC) has listed groups of agents into categories (Group 1, 2A, 2B, 3, 4) based on the strength of available evidence supporting it as a carcinogen as follows[11]:

Group 1: the agent (mixture) is definitely carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.
Group 2A: the agent (mixture) is probably (product more likely to be) carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.
Group 2B: the agent (mixture) is possibly (chance of product being) carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.
Group 3: the agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.
Group 4: the agent (mixture) is probably not carcinogenic to humans.

Cancers are classified by the cell type of origin.[12] The most common cancers are carcinomas, those derived from epithelial cells, such as the mucosal lining of the GI tract. Sarcomas are another group of cancers that arise from the connective tissue like muscle, bone, and cartilage with precursor cells called mesenchymal cells. Malignant hematopoietic cells (leukemia and lymphoma) arise from blood-forming cells in the bone marrow and or lymph tissue in the body. Other less common cell types of origin are germ cell tumors (derived from pluripotent stem cells and in tissues such as testicle and ovary), or blastomas (cancers derived from immature precursors cells or embryonic tissue).

4. Introduction to Colorectal Cancer:

Colorectal cancers are cancers that arise in the large colon, which is comprised of the Cecum/appendix, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The cancer precursor cells arise from the epithelial cells (the mucosal inner lining of the colon), and are carcinomas that have mucus gland differentiation, and are thus 'adenocarcinomas'. Annually, approximately 147,950 new cases of large bowel cancer are diagnosed, 104,610 of which are colon cancer, and the remainder are rectal cancer.[13]

Colon cancer etiology has been associated with a number of contributing factors,[14] including genetic syndromes,[4,5] high fat and red meat diet,[15-17] obesity,[10,18] sedentary lifestyle,[19,20] diabetes,[21] radiation,[22] inflammatory bowel disease,[23] asbestosis (see below),[24,25] tobacco and alcohol (see below)[26]. It is common to have more than one associated risk factor, and it is likely that having many factors will heighten the risk of developing colorectal cancer.

Colon cancers start at level of an individual cell within the mucosa (the most superficial layer in the colon that serves as the inner layer of the 'tube') that acquires genetic alteration.[27] The initial pathology is the formation, usually, of a polyp.[28] A polyp is mass of hyperplastic cells that forms a pedunculated polyp into the colon lumen. Over time, accumulation of more genetic alterations in tumor suppressor and oncogenes within cells in the polyp lead to a 'transformed' and invasive component of the polyp which is malignant.[29] Over time, the invasive cancer cell mass proliferates and can become large in its site of origin and also start to invade into deeper layers below the superficial layer of the mucosa. Over more time, the cancer can acquire more genetic mutations, and also travel through the lymphatic system and/or the blood to spread to distant sites in the body. This is called a 'carcinogenesis model', and that model of colorectal cancer and aberrant gene acquisition and cancer spread over time is well-established.[3] Staging of the cancer at the time of diagnosis determines the patients' prognosis and treatment course.[30,31]

Colon cancers are staged from I-IV:
Stage I – the cancer invades deeper into the submucosa or the next layer, the muscularis propria.
Stage II – invade from the inner surface of the colonic mucosa to the
Stage III – metastatic to regional lymph nodes.
Stave IV – metastatic to sites outside of the original site of origin and regional lymph nodes

Surgery is recommended for patients with stages I-III and a subset of 'oligometastatic' stage IV (few distant metastatic sites) with curative intent. However, the recurrence risk of stages II-IV who have undergone curative intent surgery is relatively high, and chemotherapy has shown to decrease the risk of recurrence.[32] However, stage IV non-oligometastatic is currently incurable, and treatment is considered palliative; patients ultimately will die from their cancer with a median survival of 24-36 months from diagnosis of stage IV disease.[31]

5. **Exposure:**

I reviewed the depositions of Rito Ortega, Daniel Rodriguez, Diana Rodriguez, Jose Rodriguez, and Rosamaria Gomez Rodriguez. The deposition of Rito Ortega, a coworker of Mr. Rodolfo Rodriguez while at Southern Pacific Railroad Company, indicated the use of 'magic rope' used on cold days and almost every day during the winter months where it was soaked in diesel, put on the rails, and lit to heat the rails when making repairs. Jose Rorigeuz also worked as a welder helper while Mr. Rodolfo Rodriguez was a trackman and truckdriver, and they worked together every day during his time at the railroad. Jose Rodriguez remembers 'asbestos powder from bags in the warehouse' that was used to 'mix with water and apply to bond wires on tracks'. He also recalls the use of 'magic rope.'

I also reviewed the expert report of Mr. Richard Miller, who concluded that Mr. Rodolfo Rodriguez was 'more likely than not exposed to asbestos fibers and carcinogenic diesel combustion products' and 'these exposure events would have substantially increased Mr. Rodiguez' risk for cancer'.

> "Thus, in summary, it is my professional opinion that Mr. Rudy Rodriguez was, more likely than not, exposed to asbestos fibers and carcinogenic diesel combustion products from the use of the so-called "magic rope" in his daily work repairing rails near the Sierra Blanca and Fort Hancock, TX sites. Additionally, the testimony indicates he often rode a "work train" to the site, therefore, during these time periods, Rudy Rodriguez was more likely than not exposed to the carcinogen components of diesel exhaust as well as the combustion products of the diesel fuel associated with

> the burning of "magic rope." All of these exposure events would have substantially increased Mr. Rodriguez' risk for cancer."

Finally, I reviewed the letter of Dr. Courtney Crim from 6/11/2020, where it is clear that his opinion is that Mr. Rodriguez had parenchymal and pleural abnormalities supportive of asbestos-related disease.

> "This letter summarizes the NIOSH B-read for Rodolfo Rodriguez dated 10/11/2016. The chest film was provided on a drive. The film quality was grade 2 as there was overlay of the scapulae. Parenchymal abnormalities of s/t size and shape were noted in the lower zones bilaterally of profusion 1/0. In the setting of appropriate occupational exposure, this finding is supportive of asbestos. There were pleural abnormalities observed, supportive of asbestos-related disease in the form of *en face* plaques bilaterally. The plaques showed no evidence of calcification and extended more than one-half the length of the chest wall. Other abnormalities noted included an ill-defined hemidiaphragm. Sincerely, Courtney Crim, M.D."

Based on the review of the above materials, and in addition my own qualitative review and a review of the literature, it is my opinion is that Mr. Rodolfo Rodriguez had ample exposure to asbestos during his time at Southern Pacific Railroad Company.

6. **Asbestos:** Asbestos is the commercial name for a group of hydrated magnesium silicate fibrous minerals[24]. Asbestos occurs naturally in soil and rock as long fibers. There are two major types: serpentine and amphibole. All asbestos fiber types are carcinogenic and pose a threat to human health. About 95 percent of the asbestos produced and used commercially worldwide is chrysotile, which is a serpentine fiber.[33] Asbestos has been valued for its resistance to heat and combustion. It is used in cement, ceiling and pool tiles, automobile brake linings, manufacture of train and locomotive components, and in shipbuilding. It is well known that workers (and family through indirect contact) with asbestos exposure are at significant risk for the development of both non-malignant and malignant pulmonary disease, particularly mesothelioma and lung cancer. The lifetime risk of developing mesothelioma among asbestos workers is thought to be as high as 10 percent, with classic latency of approximately three decades from time of initial exposure.[34]

   When asbestos fibers in the air are inhaled, they can stick to mucus in the throat, trachea (windpipe), or bronchi (large breathing tubes of the lungs) and might be cleared by being coughed up or swallowed. But some fibers reach the ends of the small airways in the lungs or penetrate into the outer lining of the lung and chest wall (known as the *pleura*). These fibers can irritate the cells in the lung or pleura and eventually cause lung cancer or mesothelioma. However, asbestos fibers can also be swallowed.[35] This can happen when people consume contaminated food or liquids (such as water that flows through asbestos cement pipes). And, it can also occur when people cough up asbestos they have inhaled, and then swallow their saliva. As a consequence, asbestos workers have had a demonstrated increased risk of non-mesothelioma gastrointestinal malignancies.[36-39] In the earliest report of such an association, Selikoff et al reported that, "Of 632 insulation workers, who entered the trade before 1943 and were traced through 1962, forty-five died of cancer of the lung or pleura, whereas only 6.6 such deaths were expected. Three of the pleural tumors were mesotheliomas; there was also one peritoneal mesothelioma. Four mesotheliomas in a total of 255 deaths is an exceedingly high incidence for such a rare tumor**. In addition, an unexpectedly large number of men died of cancer of the stomach, <u>colon</u>, or <u>rectum</u> (29 compared with 9.4 expected)**. Other cancers were not increased; 20.5 were expected, 21 occurred. Twelve men died of asbestosis."[38]

IARC classifies asbestos as a Group 1 carcinogen ("the agent (mixture) is definitely carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.") The National Toxicology Program (NTP) is formed from parts of several different US government agencies, including the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA). The NTP has classified asbestos as "known to be a human carcinogen", as does the US Environmental Protection Agency (EPA).[37]

7. **Asbestos and Colorectal Cancer:**

In 2009, the International Agency for Research on Cancer (IARC) evaluated asbestos and concluded, "There is *sufficient evidence* in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite). Asbestos causes mesothelioma and cancer of the lung, larynx, and ovary." "Also positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum." "For cancer of the colorectum, the Working Group was evenly divided as to whether the evidence was strong enough to warrant classification as *sufficient*." IARC stated, "All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) are *carcinogenic to humans* (Group 1)" (IARC 2012). I believe there is ample evidence that asbestos causes colon cancer. Much of this evidence has come out since 2012, and my findings are discussed below.

Preclinical Mechanistic Animal Studies:

A number of preclinical studies have been conducted supporting a causative effect of asbestos on colorectal cancer carcinogenesis. One showed that ingested chrysotile asbestos can alter regulation of DNA synthesis in the gastrointestinal mucosa in rates.[40,41] Another study evaluated the long-term effects of ingestion of asbestos on the colon in rats, and observed and concluded that i) Chrysotile fibers were seen by electron microscopy in six of ten colon specimens of rats fed and asbestos diet; ii) evidence of increased probability of asbestos-fed animals to develop colon lesions in general; iii) evidence for a cell regulator defect (lowered cAMP levels) in colon tissues of animals fed asbestos; and iv) evidence for asbestos fiber penetration of the colonic mucosa (electron microscopy studies) suggest that ingested asbestos is not inert in the colon.[42] In another study, the mucosal lining of the colon underwent changes consistent with a mineral-induced cytotoxicity after ingestion of chrysotile asbestos.[43] Asbestos fibers interact with mucosal cells of the GI tract causing damage and death of superficial cells and they also penetrate intestinal mucosa both in vivo and in vitro,[44] leading investigators to conclude that asbestos acts like a classical tumor promoter.[45] Cell proliferation caused by asbestos leads to tumor development and promotion, and the ability of chrysotile to stimulate cell proliferation, using a number of biomarkers, has been demonstrated both in vitro and after inhalation by rats.[36,46] In one study, crocidolite asbestos induced abnormal crypt foci in the colon of rats in two independent experiments ($P = 0.02$ and $P < 0.01$ compared to controls given water), and chrysotile asbestos also induced abnormal crypt foci.[46] There are some studies that have been conducted that have not demonstrated casual effect of asbestos on carcinogenesis, for example Bolton et al, although the numbers of animals evaluated in that study were low.[47] Overall and taken together, it is my opinion that, collectively, these such studies provide a mechanistic carcinogenesis effect of asbestos exposure towards colorectal cancer development.

Human Tissue Studies:

Importantly, as a follow up study to a previous report,[48] in an evaluation of asbestos-exposed workers who developed colon cancer, 38% were found to have asbestos fibers and/or bodies present in their colon tissue, while in contrast 20 unexposed colon cancer patients had no asbestos fibers and/or bodies found.[49]

Human Epidemiologic Studies:
There have been a number of epidemiologic studies over the past decades. The presence of asbestos-induced pleural plaques increased the risk of colorectal cancer among men occupationally exposed to asbestos, especially those with evidence of nonmalignant asbestos-associated radiographic changes.[50] A Canadian study demonstrated an association with a number of occupations and industries, including exposure to asbestos and other pollutants, with excess colorectal cancer risk.[51] A study of exposed subjects in Normandy, France, concluded that their study "confirmed the established relationship between asbestos exposure and pleuro-pulmonary and peritoneal cancers, our study also suggests a causal relationship between asbestos exposure and colorectal cancer.[52] While these and a number of other studies have reported association of asbestos exposure and colorectal cancer risk, some studies, such as one conducted in southeast Michigan, have not found such an association,[53] nor a meta-analysis conducted by Weiss in 1995.[54] The discrepant results of the studies could be attributed to varying factors between the studies, including amounts of the asbestos exposure and methodological differences.

Importantly, the Weiss meta-analysis was conducted 25 years ago and did not include many pertinent reports in the interim. Three new meta-analyses have since been reported. The first, by Oddone et al, evaluated manuscripts published from 1960 to 2013, and included only prospective, case-control and meta-analysis studies were as eligible for this study, and the articles had to report at least one risk or mortality estimate to be included in quantitative analysis, [standardized mortality ratio; standardized incidence ratio; hazard ratio; RR; odds ratio (OR)] and a precision estimate (95%CI) relating exposure to an industrial branch to colon, rectal, or colorectal cancer or enough data to calculate them.[55] They found that workers in the sector of repair and installation of machinery exposed to asbestos were at increased risk of colorectal cancer (RR = 1.40, 95%CI: 1.07-1.84).[55]

A second even more recent meta-analysis by Kwak et al,[56] evaluated 46 studies up to 4/2/2018, which was updated to exclude 7 redundant cohorts leaving 39 total studies.[57,58] The inclusion criteria were as follows: studies of workers exposed to asbestos, cohort studies and studies that reported mortality data for colorectal cancer (SMR or provision of data enabling calculation of the SMR). They excluded studies based on the following criteria: those that did not clearly define asbestos exposure; studies of environmental exposure to asbestos; those that reported only incidence data for colorectal cancer; studies that provided quantitative risk estimates other than the SMR (eg, RR, proportional mortality ratio, OR, HR); meta-analyses and reviews; and studies that could not be found. They concluded that occupational exposure to asbestos was significantly associated with colorectal cancer with an overall pooled standardized mortality ratio of 1.16 (95% CI: 1.05 to 1.29), that remained statistically significant even after excluding the seven overlapping studies in the reanalysis, with an overall pooled standardized mortality ratio of 1.16 (95% CI: 1.03 to 1.29).[57,58] They also concluded: "The pooled SMR for colorectal cancer was elevated in studies in which the asbestos-associated risk of lung cancer was also elevated (1.43; 95% CI: 1.30 to 1.56). This implies that the risk of colorectal cancer mortality increases as the level of asbestos exposure rises. A sensitivity analysis showed robust results and there was no publication bias. Although the effect size was small and the heterogeneity among studies was

large, our findings indicate that occupational exposure to asbestos is a risk factor for colorectal cancer."

Yet another third meta-analysis by Huang et al,[59] including 47 cohorts prior to July 2017 was recently reported. The following was their methodology, "inclusion criteria for the literature that was selected for analysis included asbestos as a clear exposure factor; standardized mortality ratio, standardized incidence ratio and hazard ratio record included, research method is a cohort study. Exclusion criteria of the literature: repeated articles or data, animal experiment data; review of records that were not original; incomplete data information; only the newest or most informative article of the same cohort." They observed and concluded, "The overall colorectal cancer SMR for synthesis cohort was 1.07 (95% CI 1.02–1.12). Statistically significant excesses were observed in exposure to mixed asbestos (SMR/SIR=1.07), exposure to production (SMR/SIR=1.11), among asbestos cement workers (SMR/SIR=1.18) and asbestos textile workers (SMR/SIR=1.11). Additionally, we determined that the SMR for lung cancer increased with increased exposure to asbestos, as did the risk for colorectal cancer. This study confirms that colorectal cancer has a positive weak association with asbestos exposure."

An important epidemiologic study not included in any of the above meta-analyses was conducted in French men.[60] The abstract from this study is as follows: "Volunteer retired workers previously exposed to asbestos were invited to participate in the "French Asbestos-Related Diseases Cohort (ARDCo)" screening program between 2003 and 2005. Additional data on risk factors for colorectal cancer were collected from the ARDCo subsample of 3,769 participants in 2011. Cases of colon and rectal cancer were ascertained each year through 2014 based on eligibility for free medical care following a cancer diagnosis. Survival regression based on the Cox model was used to estimate the relative risk of colon and rectal cancer separately, in relation to the time since first exposure (TSFE) and cumulative exposure index (CEI) to asbestos, and with adjustment for smoking in the overall cohort and for smoking, and certain risk factors for these cancers in the ARDCo subsample. Mean follow-up was 10.2 years among 14,515 men, including 181 colon cancer and 62 rectal cancer cases (41 and 17, respectively, in the ARDCo-Nut subsample). In the overall cohort, after adjusting for smoking, colon cancer was significantly associated with cumulative exposure (HR = 1.14; 95% CI: 1.04 to 1.26 for a 1-unit increase in ln-CEI) and ≥ 20-40 years since first exposure (HR = 4.67; 95% CI: 1.92, 11.46 vs. 0-20 years TSFE) and inversely associated with 60 years TSFE (HR = 0.26; 95% CI: 0.10, 0.70). Although rectal cancer was also associated with TSFE 20-40 years (HR = 4.57; 95% CI: 1.14, 18.27), it was not associated with ln-CEI, but these findings must be interpreted cautiously due to the small number of cases." The authors of this report concluded, "Our findings provide support for an association between occupational exposure to asbestos and colon cancer incidence in men."

In another epidemiologic study not included in the above meta-analyses, the Netherlands Cohort Study, a large cohort (*n* = 58,279 men, aged 55–69 years at baseline) was studied specifically addressing risk differences between relatively low and high exposure to asbestos, risk associated with cancer subtypes, the influence of potential confounders and the interaction between asbestos and smoking in relation to cancer risk.[61] Asbestos exposure was estimated by linkage to a job-exposure matrix. After 17.3 years of follow-up, 187 esophageal, 486 gastric and 1,724 colorectal cancer cases were available for analysis. This prospective population-based study showed that asbestos exposure was associated with overall gastric cancer, EAC, GNCA, total and distal colon cancer and rectal cancer.

Weighing the body of evidence available in totality, as delineated above, it is my opinion that asbestos causes colorectal cancer.

8. **Cigarette smoking and Colon Cancer:** Cigarette smoking is a known carcinogen for many cancer types. This includes colorectal cancer. Recent studies demonstrated association of the amount and duration of smoking with colorectal cancer in Korea and Norway.[26,62] Asbestos exposure acts synergistically with cigarette smoking to increase the risk of developing lung cancer 60 times over that of a similarly matched non-smoking, non-asbestos-exposed cohort. A total of 925 colorectal cancer cases and 2775 controls were included in the analysis. Odds ratios (OR) and 95% confidence intervals (CI) were computed by logistic regression models adjusting for potential confounders. In men, the risk of colorectal cancer significantly increased for heavy smokers who smoked ≥40 pack-years (OR 1.74, 95% CI 1.22-2.50), ≥40 years (OR 1.50, 95% CI 1.05-2.16), or ≥40 cigarettes/day (OR 1.92, 95% CI 1.04-3.54). Men showed a significant increase in risk, especially for rectal cancer with an increasing amount or duration of smoking. In women, distal colon cancer risk increased in smokers who smoked ≥20 years (OR 3.21, 95% CI 1.27-8.14) or ≥20 cigarettes/day (OR 4.75, 95% CI 1.09-20.57). Additionally, female smokers who smoked ≥20 cigarettes/day had an increased risk of rectal cancer (OR 6.46, 95% CI 1.64-25.46). Regarding the association of cigarettes smoked per day and the risk of rectal cancer, there was no significant difference between men and women (gender interaction p value = 0.14). Mechanistic studies demonstrating causation have demonstrated that in colon cancer cell lines, treatment with nicotine increased COX-2 expression and the release of its enzymatic product PGE_2. Moreover, nicotine-stimulated cells showed increased migratory and invasive behavior, mesenchymal markers up-regulation and epithelial markers down-regulation, nuclear translocation of the β-catenin, increase of MMP-2 and MMP-9 activity, and enhanced NF-κB expression.[63] Also, smoking is known to influence messenger RNA expression in colorectal cancers. As recent study examined current smoking, current versus never and former versus never smoking, and pack-years smoked with miRNA expression in normal mucosa as well as differential miRNA expression between paired normal and carcinoma tissue for colon and rectal tissue to determine associations between smoking and miRNA expression.[64] The study results suggested that cigarette smoking can alter miRNA expression and, given associations with CIMP high and MSI tumor molecular phenotype, it is possible that smoking influences tumor phenotype through altered miRNA expression.

   Second hand smoke is also a well-recognized risk factor for cancers, including cancers other than the lung.[65] Studies have demonstrated an association of passive smoke exposure and colorectal cancer.[66,67]

   Smoke and asbestos exposure together accentuates the risks of developing cancers.[68-71]

9. **Details of Mr. Rodolfo Rodriguez' colorectal cancer and prognosis**: At age 66, Mr. Rodriguez was diagnosed with a recto-sigmoid mass on 9/15/16, and biopsy confirmed *KRAS* mutated invasive adenocarcinoma. *KRAS* is an oncogene that is often mutated, and consequently overactive, in colorectal cancer. CT scan on 9/15/16 revealed metastatic disease to retroperitoneal para-aortic lymph nodes and also right pelvic sidewall invasion, along with seminal vesicle and prostate invasion. Therefore, he was staged as stage IV at first diagnosis. He received palliative therapy but ultimately, he died due to this cancer on 10/10/17. I am still awaiting complete medical records to opine on his exact treatment history.

   Factors that, more likely than not, each contributed to the development of his colorectal cancer include his exposure to asbestos, his documented obesity, his smoking and his diabetes. He did not have a known inherited family risk of cancer. He did not have a sedentary lifestyle as far as I can tell from the records.

I may also provide an opinion on the reasonableness or the cost of Mr. Rodriguez's cancer treatment and its necessity. I am waiting for said billing records and will amend my report if necessary.

10. **Conclusions:** Taking everything above into account, Mr. Rodolfo Rodriguez was exposed to asbestos during his time working at Southern Pacific Railroad Company. Asbestos is a known risk factor for cancer, and more likely than not was contributory to his development of his colorectal cancer, which was stage IV at the time of his diagnosis. As such, it also contributed to his death. He was treated appropriately with palliative intent for his cancer, yet as would be expected for stage IV colorectal cancer, he ultimately succumbed to his disease.

My opinions are based on medical fact and given with reasonable medical certainty. I rely on my experience in treating this and other gastrointestinal cancers, along with leading journals and reports in the field.

Best Regards,

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